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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,396	04/14/2006	Jean-Charles Schwartz	P08824US00/BAS	8440

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EXAMINER	
PIHONAK, SARAH	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
07/22/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,396	SCHWARTZ ET AL.	
	Examiner	Art Unit	
	SARAH PIHONAK	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-62* is/are pending in the application.

4a) Of the above claim(s) *34 and 39-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-33 and 35-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/28/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a 371 (national stage application) of PCT/FR04/01628, filed on 6/25/2004.

Priority

This application, filed on 4/14/2006, is a national stage application of PCT/FR04/01628, file don 6/25/2004, and claims foreign priority to Application No. 0307836, filed on 6/27/2003. Copies of the PCT and foreign applications have been received. However, the foreign application is not in English, was not accompanied by an English translation, or an English language abstract. An English language translation or abstract is respectfully requested for the foreign application. Therefore, the priority date and effective filing date given to the instant claims is 6/25/2004.

Response to Restriction Requirement

1. Applicant's election with traverse of the invention of Group I, claims 27-40, in the reply filed on 4/13/2009 is acknowledged. The traversal is on the ground(s) that Groups I-IV are all drawn to a single invention, and that the patent application EP 0982300 does not render the instant claims non-obvious or not novel. This is not found persuasive because the instant claims are made obvious over the EP 0982300 patent application, and the instant claims are drawn to different inventions. The EP '300 patent teaches H_3 histamine antagonist compounds which are used to induce wakefulness, an improvement in cognitive functioning, and a reduction in food intake (p. 2, paragraph [0002], paragraph [0016]). Additionally, the EP '300 patent application teaches that the

compounds can be administered with neuroleptic agents, to increase their effectiveness while reducing side effects associated with the neuroleptics (p. 42, paragraph [0248]). As such, the EP '300 patent renders claim 27 (of Group I) obvious. According to the PCT Rule 13.1 and 13.2, the international application will relate to a single invention or a group of inventions which are linked together by unity of invention. For unity of invention to exist, a special technical feature must exist between the different groups of inventions. The special technical features are the contributions made over the prior art. If the special technical feature (ex. composition) is not novel or is obvious in view of the prior art, the special technical feature does not exist between the groups of invention, and unity of invention is not present. Group I, claims 27-40, is drawn to a composition; Group II, claims 41, 43-51, and 54, is drawn to a method of treating undesirable side effects associated with intake of antipsychotic or antidepressant medication; Group III, claims 42, 53, and 55-61, are drawn to a method of preventing or correcting epilepsy associated with intake of antipsychotic or antidepressants; Group IV, claims 52 and 62, is drawn to a method of treating and/or preventing a mental disorder. The method claims of Groups II-IV are drawn to treating different disorders; for example, treating epilepsy is not the same as treating undesirable side effects associated with antipsychotics or depressants. There are other undesirable side effects associated with intake of antipsychotics or antidepressants that do not involve epilepsy. Additionally, the treatment of mental disorders encompasses treating a variety of disorders other than epilepsy or negative side effects associated with antipsychotic medication. Therefore, the inventions of Groups I-IV are different, and as the composition which is shared by

the groups is made obvious over the prior art, the groups are not linked by a special technical feature, and unity of invention is lacking. In response to the Applicants' statement that the International Search Report did not indicate that unity of invention was lacking, the examiner fully considered the international search report, but made an independent analysis of prior art references as well. In the Applicants' response to the election of species, olanzapine was elected as the antidepressant (compound (A)), and 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether (BF2649), as compound (B).

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 41-62 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 4/13/2009. Claims 34, and 39-40 are also withdrawn as the claims do not read on the elected species.

3. Applicants are reminded that, in the event in which the composition claims are found allowable, a rejoinder of the composition claims to the method claims will be considered.

4. Claims 27-33, and 35-38 were examined.

5. Claims 27-33, and 35-38 are rejected.

Claim Rejections-35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

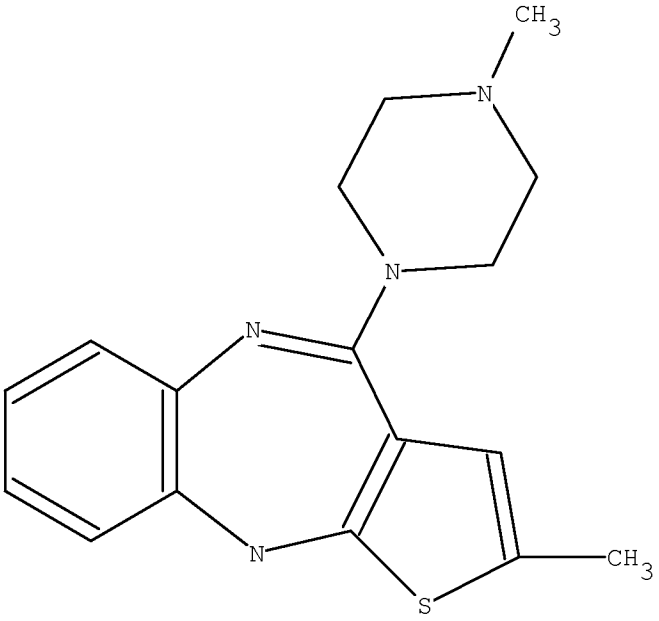
8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 27-33, and 35-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Todd, WO 00/74784 patent application publication, in view of Schwartz et. al., US 7,138,416 patent.

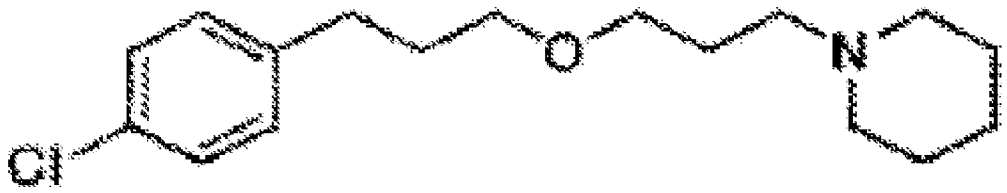
10. Instant claims 27-33 and 35-38 are drawn to a composition comprised of an antipsychotic agent, such as the elected compound, olanzapine, and an antagonist of

the H_3 histamine receptor, such as the elected compound, 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether. The elected compounds are shown below:

Olanzapine:



3-(4-chlorophenyl)propyl-3-piperidinopropyl ether:



Todd teaches that intake of antipsychotic compounds such as olanzapine are associated with negative side effects, such as weight gain (p. 1, lines 8-11, and 26-37; p. 4, lines 4-10). Todd teaches that, to reduce weight gain, antipsychotic compounds

such as olanzapine are administered with H_2 antagonists (p. 2, lines 5-20; p. 19, lines 17-19; p. 22, lines 12-24). Todd also teaches that the compounds can be administered separately, and also as a single composition (p. 22, lines 33-34; p. 23, lines 14-20). It is taught that combinations comprised of the antipsychotic agent olanzapine are preferred (p. 9, lines 4-6), and that the daily dosage of olanzapine ranges from 0.25 to 100 mg. (p. 19, lines 17-19). The preferred weight ratios of olanzapine/H_2 antagonist are taught as ranging from 1:150 (.0067) to 25:250 (.10) (p. 22, lines 12-19). The composition can be formulated as tablets, capsules, solutions, and other preparations (p. 24, lines 6-10).

Todd does not teach co-administration of olanzapine with histamine H_3 receptor inverse agonists or antagonists, such as 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether.

Schwartz et. al. teaches antagonist and agonist compounds of the histamine H_3 receptor such as 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether (Abstract; column 11, line 60; column 85-86, Table, No. 117). Schwartz et. al. teaches that 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether is effective in treating cognitive deficits associated with psychiatric pathologies, as well as obesity, attention deficits, and other disorders (column 1, lines 8-17; column 47, lines 34-38). It is also taught that the compound can be used in conjunction with psychiatric agents to improve their efficacy and reduce the side effects associated with the psychiatric drugs (column 50, lines 61-63). Oral administration is also taught (column 52, lines 6-12), as well as dosages from 10 to 500 mg. daily (column 52, lines 31-36).

Schwartz et. al. does not explicitly teach that 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether is present in a composition with olanzapine, or the specific dosage ratios of -(4-chlorophenyl)propyl-3-piperidinopropyl ether to olanzapine.

Schwartz et. al. teaches that 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether is effective in treating side effects associated with psychiatric disorders and treatment, such as obesity, cognitive deficits, attention deficits, and other illnesses. Schwartz et. al. also teaches that 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether can be used in combination with psychiatric agents to reduce side effects associated with their intake. Todd teaches that when antipsychotic agents such as olanzapine are used in combination with H_2 histamine antagonists, weight gain, which is normally associated with olanzapine intake, is reduced. It would have been obvious for one of ordinary skill in the art to formulate a composition comprised of olanzapine and 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether, because Schwartz et. al. teaches that 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether is effective in reducing weight gain and treating cognitive and attention deficits associated with psychiatric pathologies, and can be used with other psychiatric drugs, while Todd teaches that compositions comprised of olanzapine and H_2 histamine antagonists are effective in reducing weight gain associated with the drug. While Todd teaches a combination of olanzapine with H_2 antagonists rather than H_3 antagonists, such as 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether, one of ordinary skill in the art would have been motivated to substitute the H_2 antagonists of the composition with histamine H_3 inverse agonists and antagonists, such as 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether, because it is

taught that the histamine H_2 antagonists and histamine H_3 inverse agonists and antagonists are effective in lessening weight gain associated with psychiatric drugs. Therefore, an expectation of success would have been expected by substituting the H_3 antagonist, 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether, over histamine H_2 antagonists in the composition with olanzapine because both types of drugs have the same utility of reducing weight gain associated with psychiatric drug intake.

While Todd does not teach the weight ratio combination of olanzapine: 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether from 0.5 to 50 mg.:5 to 100 mg., or 3-20 mg. of olanzapine to 5 to 80 mg. of 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether, it is taught that the ratio of olanzapine:histamine H_2 antagonist ranges from 1:150 (.0067) to 25:250 (.10). The weight ratio of olanzapine: 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether as instantly claimed ranges are from 0.5 mg.:100 mg. (0.005) to 50 mg.:100 mg. (0.5), or 3 mg:80 mg. (0.375), which is within the weight ratio ranges of olanzapine:histamine H_2 antagonist taught by Todd.

Claim Rejections-Obviousness Type Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 27-33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 25-28 of copending Application No. 11/815736. Although the conflicting claims are not identical, they are not patentably distinct from each other because they encompass the same invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Instant claims 27-33 are drawn to a composition comprised of an antipsychotic or antidepressant, as well as an additional compound which is an antagonist or inverse agonist of the histamine H_3 receptor. The instant claims further include antidepressants such as mirtazapine, paroxetine, and antagonists of the histamine H_3 receptor such as the compound 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether, or a pharmaceutically acceptable salt of.

Claim 25 of the copending application is a dependent claim of claim 24, which is a dependent claim of claim 1. Claim 1 cites the HCl salt of the compound 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether. Claim 24 cites a composition comprised of the compound salt. Claims 25-28 are drawn to a composition comprised of 3-(4-

chlorophenyl)propyl-3-piperidinopropyl ether (hydrochloride salt), and additional antipsychotic and antidepressant agents such as mirtazapine, paroxetine, olazapine, and others. As claims 25-28 of the copending application are drawn to a composition comprised of 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether (hydrochloride salt) and additional antidepressant and antipsychotic agents, instant claims 27-33 and copending claims 25-28 are drawn to the same invention.

Claim Rejections-35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 30-33 and 38 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprised of pharmaceutical salts, hydrates, hydrates salts, optical isomers, racemates and enantiomers of histamine H_3 antagonists, does not reasonably provide enablement for compositions comprised of polymorphic crystalline structures of these compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. See M.P.E.P. 2164.08. The reference of Brittain, *Polymorphism in Pharmaceutical Solids*, *Drugs and the Pharmaceutical Solids*, vol. 95, pp. 1-2,7, 185, 280-280, and 321, is used in this rejection.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to compositions comprised of antipsychotics and antidepressants as well as salts, enantiomers, hydrates, and polymorphic crystalline structures of histamine H_3 receptor inverse agonists or antagonists. Thus, the claims

taken together with the specification imply that the composition can be comprised of all possible polymorphic variations of histamine H_3 inverse agonists or antagonists.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Brittain defines polymorphism as the ability of a substance to exist in two or more different crystalline phases, and that such structures have different properties and characteristics in terms of solubility, stability, and other thermodynamic, physical, and kinetic characteristics (p. 1-2; p. 7, Table 3). Brittain also teaches that because polymorphs often have differences in solubility and other properties, the biological absorption of drugs made from polymorphs can be impacted (p. 280-281). It is also taught that the existence of polymorphs would be expected to alter the bioavailability of the drug (p. 321). Furthermore, Brittain also teaches that while some polymorphs can be detected, they can not be isolated (p. 185). Therefore, as the separation of all different polymorphs can not be achieved, drugs prepared from such polymorphs are likely to have variations in stability, solubility, and bioavailability. The prior art provides evidence that as polymorphs have different properties, they are not expected to be equal in terms of stability and bioavailability as pharmaceuticals.

(5) The relative skill of those in the art:

The relative skill of one in the art is expected to be high, such as that of an MD or Ph.D.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for preparing compositions comprised of pharmaceutical salts, enantiomers, racemates, diastereomers, and optical isomers of histamine H_3 receptor inverse agonists and antagonists.

However, the specification does not provide guidance for preparing compositions comprised of all possible polymorphic crystalline structures of histamine H_3 receptor antagonists or inverse agonists.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to the evidence provided by the prior art and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims. Excessive experimentation would be required by one of ordinary skill in the art to determine which particular polymorphs of the histamine H_3 receptor antagonists and inverse agonists would be most stable in the composition and most effective in terms of solubility and bioavailability.

Information Disclosure Statement

16. The information disclosure statement (IDS) submitted on 7/28/2008 was filed. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached on Monday-Thursday 8:00 AM - 6:30 PM EST, with Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

S.P.

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